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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	9

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/046,616	OHLMEYER ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-18,24-28,30-70 and 72-85* is/are pending in the application.

4a) Of the above claim(s) *48-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,16,17,24,25,70 and 72-85* is/are rejected.

7)☒ Claim(s) *4-15,18,26,27 and 30-47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election Group II, namely pyrimidines without traverse of as to Groups I, III, IV, VI and VII but with traverse as to Group V in Paper No. 8 is acknowledged.

Claims 48-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group V.

As for Groups I, III, VI, VI, and VII, applicants have cancelled claims 2, 19-23, 29, 71, and 86-94 and have amended claims 1, 3,8-9, 12-13, 28, 30, 35-37, 39, and 44, to exclude non-elected subject matter in paper No. 8.

Claims 1, 3-18, 24-28, 30-47,70, and 72-85 are under examination.

The traversal is on the ground(s) that the search of Group V along with elected Group II would not be a serious search burden and that a single search and examination can be made. This is not found persuasive because the pharmaceutical composition claims are not simple composition of the compound of Group II but include various classes of ingredients, which are to be classified and searched. With a limited time available for each application, it would be serious search burden to search all classes of compounds embraced as additional ingredients.

The requirement is still deemed proper and is therefore made FINAL.

However, if upon examination, the claims of Group II were found to be allowable, and then examiner will rejoin the pharmaceutical composition claims and examine them.

Information Disclosure Statement

References cited in the Information Disclosure Statement (paper # 4) are made of record.

Specification

The substitute specification filed 9/17/2003 has not been entered because it does not conform to 37 CFR 1.125(b) and (c) because: addition of pages requires a substitute specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-18, 24-28, 30-47, 70, 72-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly Following reasons apply.

Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Independent claims 1 and 28 are indefinite as to the definition of A^1. It is not clear where the first choice of A^1 ends. Note there is no comma after the first choice of A^1. The same applies to the third choice. An appropriate correction is needed.
2. Again in claims 1 and 28 , in the definition of W the proviso recites "W may not be" which renders these claims indefinite and vague . Replacement of the phrase " W may not be" with "W is not" is suggested.

3. Claims 70, 72-75, and 82-84 recite the term "inappropriate" which renders the claim indefinite, as it is not clear what is intended. Specification has definition of this term and it is not clear in what context this term is to be applied.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70, 72-85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating vasculopathy and asthma, does not reasonably provide enablement for any or all bradykinin mediated conditions including those yet to be discovered as due to bradykinin and those specifically recited in claims 72-85. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following reasons apply.

The instant claims 70, 72-85 are drawn to "a method for treating a condition associated with inappropriate bradykinin receptor activity". The scope of the claims includes not only treating any or all conditions but also those conditions yet to be discovered as mediated by inappropriate bradykinin receptor activity for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on reducing inappropriate bradykinin receptor activity of the compounds provided in the specification. The instant compounds are disclosed to have ability to reduce inappropriate bradykinin receptor activity and it is recited that the instant compounds are

therefore useful in treating any or all diseases where such bradykinin activity is implicated, for which applicants provide no competent evidence. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of neurodegenerative diseases such as Alzheimer's disease, atheroscelorsis, septic shock etc. are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition such those used as additional active agents in claims 72-84". Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

In addition, the scope of claim 85 embraces a method of stimulating hair growth or preventing hair loss which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 73-75. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "inappropriate

bradykinin receptor activity effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) due to inappropriate bradykinin receptor activity claimed herein. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Kharitonov et al. Eur. Respir. J. 14(5): 1023-1027, 1999, Bagate et al., Br. J. Pharmacol. 128(8) : 1643-1650 (PubMed Abstracts provided).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating diseases that require reduction in inappropriate bradykinin receptor activity.

2) The state of the prior art: A recent publication expressed that treating disease by the inhibition of inappropriate bradykinin receptor activity is still exploratory. See Kharitonov

et al. Eur. Respir. J. 14(5): 1023-1027, 1999, Bagate et al., Br. J. Pharmacol. 128(8): 1643-1650 (PubMed Abstracts provided).

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of in reducing the inappropriate bradykinin receptor activity are unpredictable and at best limited to modulation of asthma.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to inappropriate bradykinin receptor activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical

nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claim language, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 16, 17, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arnaitz et al., WO 98/37079

Arnaitz et al. teaches several heterocyclic derivatives as nitric oxide synthase inhibitors, which include compounds claimed in the instant claims, for treating various diseases. See formula I, formula II and formula III, on page 3 and note the definition of various variable groups. Note the definition of A taught by Arnaitz et al. includes instant A groups. Also see pages 3-36 for various preferred embodiments including the pyrimidine compounds embraced in the instant claims. See entire document for detailed description. Especially see Table 1-7 on pages 94-126 for compounds made. See also specific species on pages 126-212.

Arnaitz et al. differs from the reference in not exemplifying all compounds with pyrimidine core generically embraced in the formula I, Formula II and Formula III but Arnaitz teaches representative examples of making various pyrimidine compounds with imidazolyl groups only. However, Arnaitz et al. teaches equivalency of the exemplified compounds with pyrimidine compounds in the definition of various variable groups on page 3 and the preferred embodiments on pages 3-67 and clearly contemplates making of these compounds as seen on pages 67-79. Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted the pyrimidine ring and the side chain bearing a triazoyl group as permitted by the reference and expect resulting compounds (instant

compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Allowable Subject Matter

Claims 4-15, 18, 26-27, 30-47 are objected to as being dependent upon a rejected base claim, but would be allowable, barring finding of any prior art in a subsequent search, if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Said claims would be allowed since specific species embraced in these claims are not taught or suggested by the art of record or from a search in the relevant art area.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716. The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

11/30/2003